



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/2785, 473	04/05/91	KUHN	0

1842/1021
RAYMOND J. LILLIE
CARROLL A. BYRNE, JR., RAIN, GILFILLAN, COCHIL,
STEWART & GILSTEIN
6 MEADOW PARK RD.
ROSELAND NJ 07068

EXAMINER	
STANTON, B	
ART UNIT	PAPER NUMBER
1815	

DATE MAILED: 10/21/91

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Interview Summary

Application No.
08/225,468

Applicant(s)
Kohn et al.

Examiner
Brian R. Stanton

Group Art Unit
1819



All participants (applicant, applicant's representative, PTO personnel):

(1) Brian R. Stanton

(3) _____

(2) Raymond Lillie

(4) _____

Date of Interview Oct 20, 1997

Type: ☒ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description:

Agreement ☐ was reached. ☒ was not reached.

Claim(s) discussed: All in general

Identification of prior art discussed:

n/a

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:

Applicant was contacted to discuss general aspects of enablement and level of skill in the art. In light of transfer to new examiner, applicant reviewed prosecution history and will present response based upon discussion.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. ☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.


BRIAN R. STANTON
PRIMARY EXAMINER
GROUP 1800

Examiner Note: You must sign and stamp this form unless it is an attachment to a signed Office action.

Serial Number: 08/225,478

2

Art Unit: 1804

Claims 1-26 are currently pending in U.S. Patent Application Number 08/225,478.

In a telephonic interview on 2-12-97 between Examiner's Milne and Stone and representatives Mr. Lillie and Mr. Olstein, the examiner's requested further data to overcome the 112, first paragraph rejection. Applicant's representative questioned whether the Examiner would maintain a 112 rejection based on the scope of independent claim 1 which encompasses any and all nucleic acid sequences and the treatment of any and all "disorders". The Examiner mistakenly indicated that this was not an issue and that no such rejection would be made.

Contrary to what was relayed to applicant's representative, it is noted that the Examiner's comments were in error as there does exist substantial doubt as to whether the skilled artisan could provide a therapeutic effect using any and all nucleic acid sequences in any and all disorders with a reasonable expectation of success.

Accordingly the finality of this application is hereby considered withdrawn in light of the new ground of rejection.

Claims 1-5 and 16-22 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to methods of treating severe combined immunodeficiency syndrome using therapeutic gene transfer to autologous CD34+

Art Unit: 1804

cells obtained from cord blood wherein said cells have been genetically engineered with a nucleic acid sequence encoding adenosine deaminase and further, wherein said cord blood cells are administered to a patient such that said adenosine deaminase nucleic acid is expressed in an amount sufficient to provide a therapeutic effect. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The field of gene therapy has been rapidly progressing; however, the art remains plagued by an exceedingly high level of unpredictability. The previous office actions clearly addressed and provided support for the assertion that the art was unpredictable. In fact, the field is so unpredictable that those of skill in the art could only use the ADA gene in the claimed methods to provide a therapeutic effect for the SCID condition as is evidenced by (1) the disclosure of support for ADA, and ADA alone, by virtue of its favorable characteristics and (2) the documented unpredictability in the art of gene therapy which would effectively hinder the skilled artisan from practicing the claimed invention without having to undertake undue experimentation upon using any given nucleic acid sequence.

The art clearly distinguishes favorable considerations for the specific use of ADA. For example, please see page 33 of

Art Unit: 1804

Culver et al. (one skilled in the art) "Gene Therapy: A Handbook for Physicians", Mary Anne Liebert Inc., 1994:

"The first human gene therapy experiment was initiated on September 14, 1990, for the treatment of a rare, congenital immunodeficiency disorder called adenosine deaminase (ADA) deficiency. This genetic disease was chosen as the first test of clinical gene therapy for the following reasons: (1) The gene had been cloned in 1983, and, subsequently, a large body of knowledge had accumulated about the gene and its function. ADA is considered a "housekeeping" gene because it does not require tight regulation and produces its gene product (ADA enzyme) continually within the cell. Screening studies revealed that ADA enzyme activity levels range between 10% of normal level of 50 times normal in normal individuals and are consistent with normal immune functioning without significant adverse effects. This variation in activity provides a 500 fold safety margin for vector gene expression to be effective without producing adverse effects, a property not shared by many genes. (2) **Murine retroviral vectors can efficiently and stably insert functional copies of a human ADA (hADA) gene into cultured ADA- deficient [ADA(-)] lymphocytes.** Although the goal continues to be the development of a gene transfer method for the genetic correction of bone marrow cells, engraftment of T lymphocytes alone by

Art Unit: 1804

allogeneic bone marrow transplantation can be curative and, therefore, the genetic correction of T lymphocytes may be beneficial. (3) **Insertion of a normal hADA gene into ADA(-) t lymphocytes restored normal biochemical functioning. In fact, genetically corrected T lymphocytes acquired the ability for normal growth in vitro compared to noncorrected duplicate cultures.**

(4) The group of children to be enrolled had not experienced complete immunologic reconstitution by any other form of therapy and were therefore at risk of opportunistic infection and malignancy. The results of this initial trial highlight the potential healing power of gene therapy."

At the time the application was filed, therapeutic administration of nucleic acid sequences to an animal or human subject by any route was considered by those of skill in the art to be an underdeveloped and unpredictable method of treatment, due to the difficulties in delivering therapeutically effective amounts of **any** given nucleic acid to the correct cellular compartment of the target cells *in vivo*.

Upon turning to the specification, the skilled artisan is directed to multiple types of nucleic acid sequences from which to choose to provide a therapeutic effect. Page 10 of the specification for example, provides an extended list of exogenous sequences including, but not limited to , cytokines, growth

Art Unit: 1804

factors, receptors, antisense RNA oligonucleotides, etc... . The question then remains, would the skilled artisan be able to implement the claimed method using any and all sequences disclosed and the limited guidance in the specification, and achieve a therapeutic effect without having to conduct undue experimentation. It is the position of the Examiner that the art and the specification provides sufficient guidance and direction solely for the use of the ADA gene for the treatment of severe combined immunodeficiency. The use of any and all nucleic acid sequences is not enabled by the specification nor does the art accommodate the claimed methods with a reasonable expectation of success.

For example, if the skilled artisan were to implement claim 1 using an antisense oligonucleotide sequence, there would certainly be doubt as to whether or not a therapeutic effect could be achieved in any disease state. For treatment of cells *in vitro* or *in vivo*, the chemical structure of the oligos, the length of the oligo and the binding site in the target nucleic acid, the chemical composition of the carrier used to promote cellular uptake, and the type of cell targeted, are all critical parameters which determine, in an unpredictable manner, whether or not the claimed oligomer will be successful as disclosed in the specification. Additional critical parameters for successful administration of oligos *in vivo* are the location of the targeted tissue in the treated subject, and the physical means and route

Serial Number: 08/225,478

7

Art Unit: 1804

by which the oligos are administered to the subject (Please see Uhlmann et al., pp.562-568 and Milligan et al., p.1933, for example).

Further conclusive evidence can be found in Applicant's own work, kindly see page Kohn et al., Nature Medicine, 1(10), October 1995, page 1021, column 2:

"The successful application of gene therapy to other haematologic disorders where the transduced progenitors do not have a selective advantage, such as hemoglobinopathies, lysosomal storage disorders, and AIDS, **will require more efficient gene transfer.** These advances **will require better understanding** of the biology of haematopoietic stem cells and the cytokines that regulate their proliferation."

~~It is respectfully submitted for the record that this is~~ applicant's own work. It is further submitted that this article was published approximately 17 months after the filing date of the present application and continues to state that further experimentation is required in order to use the claimed invention to treat diseases other than scid using genes other than ADA.* It is therefore submitted that this provides sufficient evidence to doubt that any and all genes could be used to treat any and all diseases without having to undertake undue experimentation.

Art Unit: 1804

It is well known in the art that while some progress has been made toward human gene therapy, only a handful of clinical trials and very limited success have been reported to date. It is noted that the **unpredictability** of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of a claim. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). With respect to a prima facie case of nonenablement, while a single embodiment may provide broad enablement in cases involving predictable factors, in cases involving unpredictable factors, such as physiological activity, a further showing is required. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970).

It is therefore concluded that in light of the quantity of experimentation necessary, the lack of adequate direction or guidance presented, the lack of correlatable working examples, the nature of the invention, the state of the prior art with its recognized unpredictability, and the breadth of the claims, it would require undue experimentation for others skilled in the art to practice the invention.

Claims 1-5 and 16-22 stand rejected under 35 U.S.C. § 112, first paragraph, as being indefinite for failing to particularly

Serial Number: 08/225,478

9

Art Unit: 1804

point out and distinctly claim the subject matter which applicant regards as the invention.

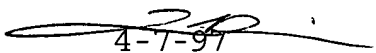
Claims 6-15 and 23-26 are allowable at this time for reasons of record.


Any inquiry concerning this communication from the examiner should be directed to Andrew Milne, whose telephone number is (703) 308-4213. The examiner can normally be reached from 7:00 to 4:00 (Eastern Standard Time) Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasmine Chambers, can be reached at (703) 308-2035. The fax number for art unit 1804 is (703) 308-4312.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is (703) 308-0196.

Andrew Milne


4-7-97


JASEMINE C. CHAMBERS, PHD.
SUPERVISORY PATENT EXAMINER
GROUP 1800